

## PRELIMINARY COMMUNICATION

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# Exploding vesicles

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## Abstract

While studying fatty acid vesicles as model primitive cell membranes, we encountered a dramatic phenomenon in which light triggers the sudden rupture of micron-scale dye-containing vesicles, resulting in rapid release of vesicle contents. We show that such vesicle explosions are caused by an increase in internal osmotic pressure mediated by the oxidation of the internal buffer by reactive oxygen species (ROS). The ability to release vesicle contents in a rapid, spatio-temporally controlled manner suggests many potential applications, such as the targeted delivery of cancer chemotherapy drugs, and the controlled deposition of functionalized nanoparticles in microfluidic devices. Recent observations of light-triggered lysosome rupture *in vivo* suggest the possibility that a common mechanism may underlie light-triggered vesicle explosions and lysosome rupture.

## Findings

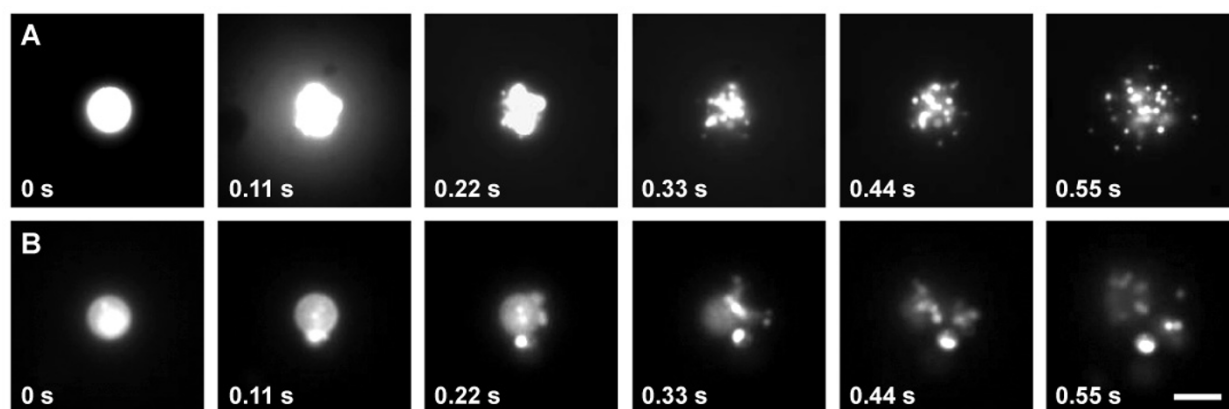
Vesicles are bilayer membrane structures that encapsulate an internal aqueous compartment. Fatty acid vesicles have been studied as models of primitive cell membranes at the origin of life [1-7], and phospholipid vesicles (liposomes) have been widely studied as models of modern cell and organelle membranes [8,9] and as drug delivery vehicles [10-12]. We first observed the phenomenon of “exploding vesicles” during microscopic observations of large (approximately 4  $\mu\text{m}$  in diameter) oleate vesicles containing 10 mM HPTS (8-hydroxypyrene-1,3,6-trisulfonic acid trisodium salt, a water-soluble, membrane-impermeable fluorescent dye), in 0.2 M N-bicine buffer, pH 8.5. The vesicles were prepared by extrusion and dialysis, so that the fluorescent dye was present only inside the vesicles while the buffer was present in both inner and outer solutions [13]. To our surprise, we observed that these vesicles suddenly exploded shortly (approximately 0.5 sec) after being exposed to intense illumination from a metal halide lamp (estimated irradiance 2.5 W/mm<sup>2</sup>), and released their encapsulated dye along with smaller internal vesicles (Figure 1A; Additional File 1 Figure S1; Additional File 2). The actual vesicle rupture appeared to take place in < 2 ms (3 frames in a recording from a high-speed camera; Additional File 3); this estimate is an upper limit

because of the time required for diffusion of the released dye away from the vesicle. We observed similar vesicle explosions using vesicles containing different internal fluorescent dyes, such as calcein and Rose Bengal (a photodynamic therapy drug).

To distinguish between physical rupture and rapid permeabilization of the vesicle membrane, we labeled the vesicles with a membrane-localized dye (Rh-DHPE, Lissamine rhodamine B 1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine). Upon illumination, we observed that the vesicle membrane burst open on one side and then quickly recoiled (Figure 1B; Additional File 4). When using slightly lower illumination intensity, we observed the gradual rupture of the multiple layers of multilamellar vesicles, starting from the outer layers and progressing to the inner layers (Additional File 5). We tested several possible explanations for the physical mechanism of light-triggered vesicle explosion. Numerical calculations suggested that rapid temperature rise due to dye-mediated absorption of incident light energy was unlikely to be relevant, since the maximum temperature increase in a vesicle was estimated to be < 0.1° C (Additional File 1 Figure S2). We then considered the hypothesis that reactive oxygen species (ROS) generated by the illumination of fluorescent dyes such as HPTS might react with vesicle membrane components or vesicle contents [14,15], leading to vesicle rupture. We tested this model by adding 10 mM DTT (dithiothreitol, a reducing agent) to the vesicle suspension, in order to consume free oxygen and scavenge ROS as they were produced [16]. Under these conditions we no longer

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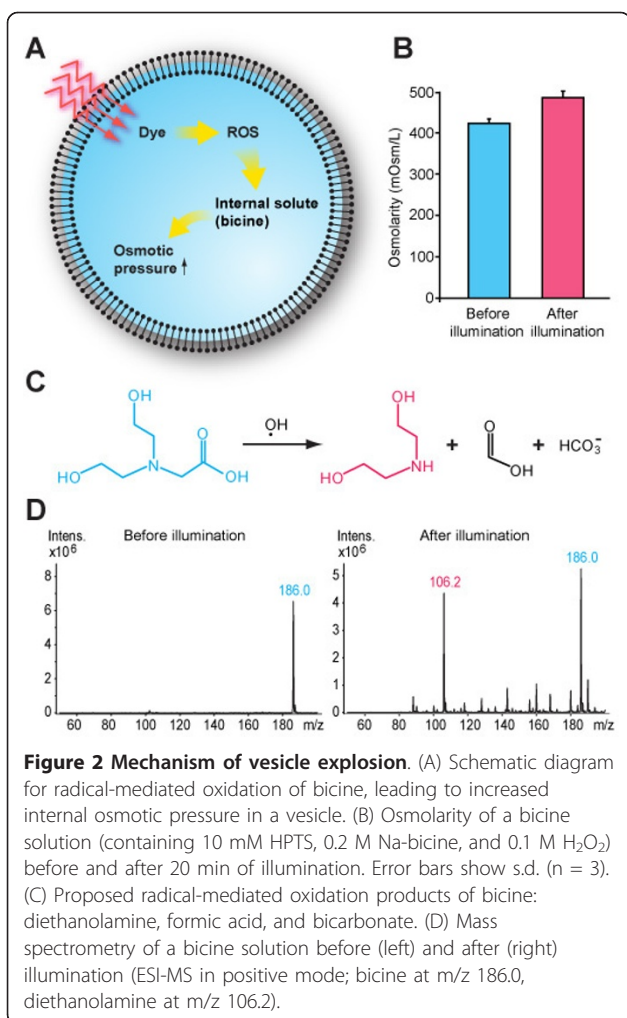
**Figure 1 Exploding vesicles.** (A) A sequence of images showing the explosion of an oleate vesicle (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5) under intense illumination, releasing the encapsulated dye (0.11 sec) and smaller internal vesicles (0.33 sec). (B) A sequence of images showing the explosion and membrane rupture of an oleate vesicle labeled by a membrane-localized dye (Rh-DHPE, vesicle containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5) under intense illumination at the excitation wavelength for HPTS (Additional File 4). Scale bar, 5  $\mu$ m.

observed vesicle explosions, even under intense illumination.

We then asked whether the vesicle membrane, composed of an unsaturated fatty acid, oleic acid, or the encapsulated vesicle contents, e.g., the internal buffer bicine (*N,N*-bis(2-hydroxyethyl)glycine), were the target of the radical-mediated oxidation. Oxidation of the unsaturated oleate hydrocarbon chain to either an epoxide or a hydroxylated derivative would certainly destabilize the membrane, and could lead to rapid vesicle rupture. If oleate was the target of oxidative damage, then replacing oleate with a saturated amphiphile should prevent vesicle explosion. However, when we prepared vesicles with a saturated fatty acid/fatty alcohol mixture (decanoate:decanol (2:1) vesicles containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5), we still observed vesicle explosions. In contrast, replacing the internal bicine buffer with glycineamide or Tris buffer completely prevented vesicle explosions, suggesting that the radical-mediated oxidation of the internal buffer was responsible for the vesicle explosions. To further test the idea that it was oxidation of the *internal* solute that was critical, we placed equal concentrations of the fluorescent dye (10 mM HPTS) inside and outside of oleate vesicles (in 0.2 M Na-bicine, pH 8.5; vesicles were labeled by a membrane-localized dye, Rh-DHPE). The presence of external HPTS completely prevented vesicle explosions, even after intense illumination for 10 sec (Additional File 1 Figure S3). Thus, oxidation of the internal buffer in the absence of oxidation of the external buffer is essential for vesicle explosions. We tested this idea further by performing cross-mixing experiments, in which vesicles prepared in 0.2 M Na-bicine buffer (containing 10 mM HPTS, pH 8.5) were diluted into 0.2 M

Na-glycinamide buffer (pH 8.5), and vice versa. We observed vesicle explosions only when the vesicles contained bicine and the external solution did not. Thus, the internal buffer solute, bicine, is the key target molecule leading to vesicle explosions.

We next asked how the products of the radical-mediated oxidation of bicine could lead to vesicle explosions. It has been shown previously that ROS can oxidize bicine to diethanolamine, formic acid, and bicarbonate [17]. We hypothesized that this pathway of oxidative degradation could increase the internal osmotic pressure of a vesicle, leading to rupture of the membrane (Figure 2A, C). To test this model, we placed 50  $\mu$ l of a solution containing 0.2 M Na-bicine (pH 8.5), 10 mM HPTS, and 0.1 M  $H_2O_2$  in a microcentrifuge tube, and illuminated the sample through a  $480 \pm 20$  nm filter for 20 min. We used 0.1 M  $H_2O_2$  as an additional source of oxygen for this bulk solution reaction; in the case of vesicles, oxygen molecules from the surrounding solution can enter the vesicle by diffusion and membrane permeation. We analyzed the sample, before and after illumination, by mass spectrometry and detected diethanolamine after illumination, one of the predicted oxidation products of bicine (we could not detect formic acid due to its lower molecular weight) (Figure 2D). NMR analysis of the products of bicine degradation suggested the presence of both diethanolamine and formic acid after illumination (Additional File 1 Figure S4) in amounts corresponding to oxidation of approximately 10% of the bicine. We propose a possible mechanism for the radical-mediated oxidation of bicine based on the current model experiment and previous studies (Additional File 1 Figure S5) [17-19]. Additional experiments would be required to test this mechanistic



**Figure 2 Mechanism of vesicle explosion.** (A) Schematic diagram for radical-mediated oxidation of bicine, leading to increased internal osmotic pressure in a vesicle. (B) Osmolarity of a bicine solution (containing 10 mM HPTS, 0.2 M Na-bicine, and 0.1 M H<sub>2</sub>O<sub>2</sub>) before and after 20 min of illumination. Error bars show s.d. (n = 3). (C) Proposed radical-mediated oxidation products of bicine: diethanolamine, formic acid, and bicarbonate. (D) Mass spectrometry of a bicine solution before (left) and after (right) illumination (ESI-MS in positive mode; bicine at m/z 186.0, diethanolamine at m/z 106.2).

hypothesis, and to show that it operates during the illumination of vesicles containing fluorescent dyes.

To correlate buffer degradation with increased osmotic pressure, we compared the osmolarity of samples (0.2 M Na-bicine, 10 mM HPTS, and 0.1 M H<sub>2</sub>O<sub>2</sub>, pH 8.5) before and after illumination, using a vapor pressure osmometer, and observed an increase of approximately 60 mOsm/L (Figure 2B), corresponding to the fragmentation of approximately 15% of the bicine solute. The pH of the solution did not change significantly, presumably due to the buffering effect of the remaining bicine. At pH 8.5, approximately 99.5% of dissolved carbon dioxide (as H<sub>2</sub>CO<sub>3</sub>, pK<sub>a</sub> 6.35) exists in the form of bicarbonate (HCO<sub>3</sub><sup>-</sup>), contributing predominately to the increased osmotic pressure as opposed to gas-induced volume expansion. Thus, photochemically induced oxidative degradation of bicine can and does lead to an increase in osmotic pressure.

We then determined how much of an osmotic gradient would be required to cause vesicle membrane

rupture by diluting vesicles into a hypotonic solution through a micropipette (Additional File 1 Figure S6; Additional File 6). We found that an osmotic gradient of only approximately 20 mOsm/L is sufficient to rupture the outer membranes of oleate vesicles of approximately 4 μm in diameter. We estimated that the rupture surface tension for oleate membrane is approximately 12 dyn/cm, as calculated from the osmotic pressure gradient required for rupture and the Young-Laplace equation, accounting for vesicle swelling from a relaxed to a swollen spherical shape (Additional File 1) [20,21], a result which is in good agreement with the previously reported value (10 dyn/cm) determined in experiments with 100 nm vesicles [20]. As a further test of the osmotic rupture model, we examined the size dependence of vesicle explosions. For a given cross-membrane osmotic gradient, larger vesicles are subject to greater surface tension and therefore are expected to explode more rapidly than smaller ones under the same illumination intensity (Additional File 1). We prepared a population of polydisperse oleate vesicles with diameters ranging from 100 nm to 10 μm (all containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5), and observed that the larger (> 3 μm in diameter) vesicles exploded rapidly under intense illumination while the smaller vesicles remained intact, until the encapsulated HPTS gradually became photobleached (Additional File 1 Figure S7; Additional File 7). As a final test of the osmotic rupture model, we diluted vesicles into a hypertonic solution (containing 0.5 M sucrose and 0.2 M Na-bicine, pH 8.5), whereupon they shrank due to water efflux. After exposure to intense illumination, the vesicles swelled and returned to their original spherical shape, but failed to explode. Taken together, the above experiments suggest that photo-degradation of only approximately 5% of the bicine buffer would be sufficient to cause vesicle explosion. Calculations based on photon flux, dye concentration and extinction coefficient, and the quantum yield of ROS generation suggest that sufficient ROS to degrade that amount of bicine would readily be generated in < 0.5 sec (Additional File 1).

Having developed a reasonable mechanistic explanation of the vesicle explosion phenomenon, we turned to the exploration of practical applications of the ability to release vesicle-encapsulated substances in a rapid, spatio-temporally controlled manner. A major question in treating cancer is how to localize the release of cytotoxic drugs to target tumors [11], thus reducing systemic toxicity. By delivering a drug such as a chemotherapeutic agent through photoactivation, exploding vesicles may be used to localize drug release and strengthen the effectiveness of cancer treatments. As a proof-of-principle, we designed photoactivable vesicles containing chemotherapy drugs (cisplatin or carboplatin) and used an

*in vitro* cell culture system to test the effectiveness of this potential photoactivated delivery system (Additional File 1 Figure S8). This delivery method, because of its ability to rapidly (< 1 sec) rupture the membrane and release vesicle contents, could serve as an alternative to several existing methods for photoactivated membrane permeabilization and drug delivery (Additional File 1) [10,22-24]. One potential problem with this approach is that the generation of large amounts of ROS that lead to vesicle rupture may limit the variety of drugs that can be delivered. Using drug-conjugated nanoparticles [25] to carry and protect cargo drugs from immediate radical oxidation during photoactivation may help to resolve this issue. It may also be possible to design different photochemical processes that increase the internal osmotic pressure and induce vesicle membrane rupture without generating ROS. Alternatively, it may be possible to harness the ROS generated by exploding vesicles to kill cancer cells. Exploding vesicles can also be used to release functionalized nanoparticles for applications such as localized surface modification of a microfluidic channel. In a proof-of-principle experiment, we encapsulated biotin-coated fluorescent nanoparticles (40 nm in diameter) in oleate vesicles (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5), which were lysed under intense illumination in a microfluidic channel (Additional File 1 Figure S9A, B, C; Additional File 8). This process allowed the released biotin-coated fluorescent nanoparticles to attach to the streptavidin-coated surface of a microfluidic channel [26] within the illuminated region of approximately 100  $\mu\text{m}$  in length (Additional File 1 Figure S9D). More generally, the ability to release vesicle-encapsulated substances in a highly spatio-temporally controlled manner provides an alternative to the chemical release of caged derivatives of small molecules [27], such as for studying bacterial chemotaxis and neuronal signaling (Additional File 1 Figure S10).

Other examples of vesicle leakage or bursting following illumination have been reported, which may result from phenomena similar to those reported here. For example, prolonged illumination (minutes to hours) of phospholipid GUVs containing membrane-localized fluorescent dyes led to a gradual increase in membrane tension, ultimately leading to a cycle of opening of a transient pore in the membrane, followed by leakage of vesicle contents and pore closing [28]. In another case, 500 nm LUVs containing a high (self-quenching) concentration of calcein, docked to a supported lipid bilayer by a SNARE complex, were occasionally observed to burst during illumination [29]. In neither of these cases was the mechanism driving increased membrane tension and subsequent leakage or bursting investigated.

Recent observations of light-triggered rupture of dye-containing lysosomes *in vivo* may be related to the phenomena that we have described above. Lysosomes stained with acridine orange in rat and human astrocytes exploded under laser illumination [30], and acridine orange stained lysosomes in human fibroblasts ruptured under intense illumination [31]. We have observed the explosion of autofluorescent lysosomes (containing lipofuscin pigments ("aging pigments")) [32] in adult/aging *C. elegans* under intense UV ( $360 \pm 20$  nm) illumination (Additional File 1 Figure S11; Additional File 9), suggesting that similar phenomena might occur in a variety of cells and animal models. Additionally, studies on photodynamic therapy have revealed that certain photosensitizers accumulate in lysosomes and can cause lysosome rupture and release of lysosomal enzymes during photodynamic treatments, leading to cell necrosis [33]. Most current models suggest that either temperature increase or the oxidation of lysosome membranes leads to lysosome rupture [34]. Our study of the *in vitro* exploding vesicle system suggests another possible mechanism for oxidative stress induced lysosome rupture: oxidation of lysosomal internal solutes (such as peptides and amino acids) leading to increased osmotic pressure and ultimately membrane rupture. Future experiments to analyze lysosomal internal solutes and to address how their oxidation may increase the internal osmolarity of lysosomes may help to elucidate the mechanism of oxidative stress induced lysosome rupture.

## Additional material

**Additional file 1: Additional information.** This file includes Methods, Additional Text, and Additional Figures [35-41].

**Additional file 2: Exploding vesicles.** This real-time movie shows that oleate vesicles (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5) exploded shortly (~0.5 sec) after being exposed to intense illumination (QuickTime; 9 FPS; 1 MB). Scale bar, 10  $\mu\text{m}$ .

**Additional file 3: High-speed movie of an exploding vesicle.** This high-speed (played at 1/100 actual speed) movie shows an oleate vesicle (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5) exploding under intense illumination (QuickTime; 15 frames per 10 ms; 4 MB). Scale bar, 10  $\mu\text{m}$ .

**Additional file 4: Exploding vesicle labeled by a membrane dye.** This real-time movie shows an oleate vesicle (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5, labeled by a membrane-localized dye (Rh-DHPE)) that exploded and ruptured its membrane, under intense illumination at the excitation wavelength for HPTS (QuickTime; 9 FPS; 1 MB). Scale bar, 10  $\mu\text{m}$ .

**Additional file 5: Explosion of a multilamellar vesicle.** This real-time movie shows the gradual rupture of multiple layers of vesicle membranes, starting from the outer layers of an oleate vesicle (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5) and progressing to the inner layers (QuickTime; 9 FPS; 2 MB). Scale bar, 10  $\mu\text{m}$ .

**Additional file 6: Critical osmotic gradient for membrane rupture.** This real-time movie shows a vesicle being diluted into a hypotonic solution through a micropipette. The outer membranes ruptured, and



the smaller internal vesicles were released (under low intensity illumination for imaging) (QuickTime; 9 FPS; 2 MB). Scale bar, 10  $\mu$ m.

**Additional file 7: Size dependence of vesicle explosions.** This real-time movie shows that in a population of polydisperse oleate vesicles (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5), under intense illumination, the larger (> 3  $\mu$ m in diameter) vesicles explode rapidly while the smaller ones remain intact (QuickTime; 9 FPS; 3 MB). Scale bar, 10  $\mu$ m.

**Additional file 8: Nanoparticle release from exploding vesicle.** This real-time movie shows that an oleate vesicle (containing 10 mM HPTS, in 0.2 M Na-bicine, pH 8.5) containing encapsulated biotin-coated fluorescent nanoparticles (40 nm in diameter) exploded shortly after being exposed to intense illumination, releasing a cloud of nanoparticles, which attached to a streptavidin-coated glass surface (QuickTime; 9 FPS; 3 MB). Scale bar, 10  $\mu$ m.

**Additional file 9: Lysosome explosions in adult *C. elegans*.** This real-time movie shows that under intense UV (360  $\pm$  20 nm) illumination, autofluorescent lysosomes explode, releasing the lysosomal contents (QuickTime; 5 FPS; 10 MB). Scale bar, 10  $\mu$ m.

## Acknowledgements

We thank M. Elenko, J. Irazoqui, R. Irwin, T. Kawate, C. Lin, A. Luptak, S. Mansy, C. Wong, N. Zhang, and S. Zhang for their helpful discussions and comments on the manuscript. We especially thank N. Zhang for his assistance in performing the NMR experiments and interpreting the results, and J. Irazoqui for his assistance with the *C. elegans* experiments. J.W.S. is an Investigator of the Howard Hughes Medical Institute. This work was supported in part by grant EX802-0031-0018 from the NASA Exobiology Program to J.W.S.

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## Authors' contributions

All experiments were performed by TFZ. Both authors designed the experiments, discussed the results and wrote the paper. Both authors have read and approved the publication of the final version of this paper.

## Competing interests

The authors declare that they have no competing interests.

Received: 3 October 2011 Accepted: 1 December 2011

Published: 1 December 2011

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doi:10.1186/1759-2208-2-4

Cite this article as: Zhu and Szostak: Exploding vesicles. *Journal of Systems Chemistry* 2011 **2**:4.

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